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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 10/587,386
Filing Date: May 3, 2007
Appellant(s) : Stefan Schorling

Rhea C. Nersesian
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 26, 2011 appealing from the Office action mailed December 23, 2010.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Schmidt et al. "Parvovirus B19 DNA in plasma pools and plasma derivatives". Vox Sanguinis Vol. 81, No. 4 (2001), pp. 228-235.

Harder et al. "New LightCycler PCR for rapid and sensitive quantification of Parvovirus B19 DNA guides therapeutic decision-making in relapsing infections". J. Clinical Microbiol. Vol. 39, No.12 (2001), pp. 4413-4419.

Hemauer et al. "Sequence variability among different parvovirus B19 isolates". J. General Virology Vol. 77 (1996), pp. 1781-1785.

Lowe et al. "A computer program for selection of oligonucleotide primers for polymerase chain reactions". Nucleic Acid Res. Vol. 18, No. 7 (1990), pp. 1757-1761.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 4, 5 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Vox Sanguinis (2001) Vol.81, No.4, pp.228-235), in view of Hemauer et al. (J. General Virology (1996) Vol.77, pp.1781-1785) and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp. 1757-1761).

Regarding claims 4, 5, 8 and 10, Schmidt discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of

primers comprising a first and a second primer, (c) amplifying the target nucleic acid, (d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid, and (e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid (see p. 229, "Quantitative TaqMan PCR" where Schmidt discusses the method including two primers and a doubly labeled probe within the NS1 region. Schmidt states the primers and probes are within nucleotides 2030 to 2171 of the B19 Genome).

Regarding claim 9, Schmidt discusses the method wherein the target nucleic acid in step c) is amplified with a template-dependent DNA polymerase (see p. 229, "Quantitative TaqMan PCR" where Schmidt uses TaqGold Polymerase).

Schmidt does not discuss the method whereby the first primer has a nucleic acid sequence consisting of SEQ ID NO: 15, and whereby the second primer consists of SEQ ID NO: 17. Schmidt also does not discuss the method wherein the probe has the sequence consisting of SEQ ID NO: 11. However, Schmidt discusses primers and a probe that are nearby to such sequences as the instant SEQ ID NOs: 11, 15 and 17, located within the same NS1 region of the Parvovirus B19 genome.

Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO: 11 (nucleotides 147-172), SEQ ID NO:15 (nucleotides 121-140) and SEQ I D NO: 17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically

included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

One of ordinary skill in the art would have been motivated to modify the method of Schmidt to use primers of SEQ ID NO: 15 and 17 and a probe sequence of SEQ ID NO: 11 because Schmidt demonstrates the benefits of designing and using similar primers and a probe targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer sequences of SEQ ID NO: 15 and 17 and probe sequences of SEQ ID NO:11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO: 15 and 17, and probe sequences of SEQ ID NO: 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal method. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Schmidt to substitute for similar and equivalent primers and a probe derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the

art at the time of the invention to carry out the claimed methods and use the claimed primer and probe therein.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was “obvious to try” by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding “obvious to try”, the Court stated:

“A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.”

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes “Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents.

An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2 lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

4. Claims 4-7, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harder et al. (J. Clin.Microbiol. (2001) Vol.39, No.12, pp.4413-4419), in view of Hemauer et al. (J. General Virology (1996) Vol.77, pp.1781-1785) and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp. 1757-1761).

Regarding claims 4-7, and 10, Harder discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid by contacting the sample with the said pair of primers to produce an amplification product if the target nucleic acid is present in said sample, (d) contacting said sample with the pair of probes, wherein the members of said pair of probes hybridize to said amplification product within no more than five nucleotides of each other, wherein the first probe of said pair of probes is labeled with a donor fluorescent label and wherein the second probe of said pair of probes is labeled with a corresponding acceptor fluorescent label; and (e) detecting the presence or absence of fluorescence resonance energy transfer between said donor fluorescent label of said first probe and said acceptor fluorescent label of said second probe, wherein the presence of fluorescence resonance energy transfer is indicative of the presence of the target nucleic acid in the sample, and wherein the absence of fluorescence resonance energy transfer is indicative of the absence of the target nucleic acid in the sample (see p. 4414, "LC-depedent amplification of B19 DNA", lines 25-40, where Harder uses NS-1a and NS-1a' as primers and two adjacent donor/acceptor probes in a real-time FRET lightcycler PCR assay; and Figures 1 and 2).

Regarding claim 9, Harder discusses the method where amplification is performed using the FastStart SYBR green kit from Roche, which uses a FastStart Taq DNA polymerase that is a modified form of thermostable recombinant Taq DNA

polymerase (Taq is a template-dependent DNA polymerase) (see p .4414, "LC-dependent amplification of B19 DNA").

Harder does not discuss the method whereby the first primer has a nucleic acid sequence consisting of SEQ ID NO: 15, and whereby the second primer has a nucleic acid sequence consisting of SEQ ID NO: 17. Harder also does not discuss the method wherein the probe has a sequence consisting of SEQ ID NO: 11. However, Harder teaches primers and probes that are nearby to such sequences as the instant SEQ ID NO: 11, 15 and 17 that are located within the NS1 region of the Parvovirus B19 genome.

Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO: 11 (nucleotides 147-172), SEQ ID NO: 15 (nucleotides 121-140) and SEQ I D NO: 17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

One of ordinary skill in the art would have been motivated to modify the method of Harder to use primers of SEQ ID NO: 15 and 17 and a probe sequence of SEQ ID NO: 11 because Harder demonstrates the benefits of designing and using similar primers and probes targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer

sequences of SEQ ID NO: 15 and 17 and probe sequences of SEQ ID NO: 11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO: 15 and 17, and probe sequences of SEQ ID NO: 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal method. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Harder to substitute for similar and equivalent primers and probes derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer and probe sequences therein.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was “obvious to try” by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding “obvious to try”, the Court stated: “A person of ordinary skill is also a person of ordinary creativity, not an automaton.

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.”

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes “Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).”

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a

known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2 lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

5. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4, 5 and 8-10 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4-7, 9 and 10 above and further in view of Andrus et al. (US 7,348,164).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the primer and/ or the probe comprise a modified nucleotide or a non-nucleotide compound.

However, Andrus demonstrates that the use of modified nucleotides or non-nucleotide compounds in primers and probes which detect Parvovirus B19 sequences

was conventional in the art at the time of the invention (see abstract, Figures, and col.9, lines 59-67). Therefore, one of skill in the art would have had a reasonable expectation of success in modifying the primer and/or probe of Schmidt, as modified by Hemauer and Lowe, or Harder, as modified by Hemauer and Lowe, to include a modified nucleotide or a non-nucleotide compound since Andrus demonstrates it was conventional to do in the art at the time of the invention. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and use the claimed primers and/or probe comprising modified nucleotides or non-nucleotide compounds therein.

6. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4, 5 and 8-10 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4-7, 9 and 10 above, and further in view of Mosquera et al., "Simultaneous Detection of Measles Virus, Rubella Virus, and Parvovirus B19 by Using Multiplex PCR," J. Clin. Micro., 2002, Vol.40, No.1, pp.111-116.

The teachings of the primary references are discussed above. These references do not discuss the method wherein other target nucleic acids are detected in the same reaction.

However, it was conventional in the art to conduct multiplex PCR assays where Parvovirus B19 is detected within the multiplex, as demonstrated by Mosquera et al.

Mosquera explains that it is beneficial to detect all three together as the rash illness caused by Rubella Virus, and Parvovirus B19 is easily confused with measles virus infection and differential diagnosis is recommended for surveillance activities (see abstract and pg.11, right column, first full paragraph). Therefore, one of skill in the art would have had a reasonable expectation of success in modifying the method of either one of Schmidt, as modified by Hemauer and Lowe, or Harder, as modified by Hemauer and Lowe, to detect multiple target nucleic acids with Parvovirus B19 since Mosquera demonstrates that it was conventional in the art to conduct multiplex assays including Parvovirus B19 for the added benefit of being able to distinguish between viral infections which cause similar physical symptoms. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and also detect other target nucleic acids therein.

(10) Response to Argument

Introduction

This application involves one central 35 U.S.C. 103(a) rejection of a single base claim (claim 4) and depends upon whether all of the claim elements are taught or suggested by the combination of either Schmidt, Hemauer and Lowe or Harder, Hemauer and Lowe and whether there is motivation to combine the references, particularly with regard to the limitations for primer and probe sequences. All other pending claims are dependent upon claim 4 and are not argued separately in the brief.

Issue – Does the combination of Schmidt, Hemauer and Lowe or Harder, Hemauer and Lowe render the claims *prima facie* obvious?

Legal Standard

The legal standard for obviousness is based upon the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

***Prima Facie* Case**

The *prima facie* case of obviousness is set forth in the rejection given above. The first consideration is whether the combined references teach each of the limitations of the claims, particularly with regard to the limitations for primer and probe sequences.

Appellant argues that the combined teachings of Schmidt, Hemauer and Lowe or Harder, Hemauer and Lowe fail to disclose the specific sequences consisting of SEQ ID NOS: 15 and 17 (primers) and 11 (probe) useful in a method for the detection of a target sequence comprising the nucleic acid sequence of parvovirus B19 in a sample. In particular, Appellant argues that the claimed oligonucleotides and those taught by the prior art are not homologous and are not "structural homologs" simply because the claimed sequences are homologous to sequences taught by Hemauer. Appellant argues that the primers taught by Schmidt and Hemauer, though targeting the NS1 region of parvovirus B19, are 15-22 or 211-307 bases away, respectively, from the

claimed sequences, and thus have 0% homology to the claimed sequences, with the exception of primer TP1 of Schmidt which overlap SEQ ID NO: 15 by five bases. Likewise, Appellant argues that the primers taught by Harder and Hemauer, though also targeting the NS1 region of parvovirus B19, are greater than 400 bases away from the claimed sequences, and therefore also have 0% homology to the claimed sequences. Appellant thus argues that the different oligonucleotide sequences of the prior art and the instant claims are not “equivalents" and do not possess similar properties and would not be expected to perform equivalently in detecting viral target sequences, and therefore the Examiner is in error in citing MPEP 2144.06, "Substituting equivalents for the same purpose", since the different oligonucleotide sequences are directed to different target sequences that may be better or worse for oligonucleotide design and viral detection.

The Examiner relied on Schmidt as a primary reference since this reference teaches detection of parvovirus B19 using primers and a dual-labeled probe for use in a real-time PCR assay. Though Schmidt does not teach any of the specific primers or probes cited in claim 4, the reference does teach primers and a probe that bind within nucleotides 2030 to 2171 of the NS1 region, including forward primer TP1 that shares five nucleotides of overlap with claimed SEQ ID NO: 15. Furthermore, though Hemauer also fails to teach the specific primers or probes cited in claim 4, this reference teaches the NS1 region spanning genome positions 1924-2317 that include the binding sites of the claimed oligonucleotides, as well as a primer set taught by Hemauer that resides within 307 bases of the claimed primer sequences. Though Schmidt does not teach the

NS1 sequence itself, both Schmidt and Hemauer teach primers that can amplify this sequence, and therefore it is obvious to combine the teachings of Schmidt for diagnostic detection of parvovirus B19 in a sample with a teaching such as Hemauer that provides the NS1 sequence that can be used for primer and probe design. With regard to structural homologs or “equivalents" derived from sequences suggested by the prior art, the Examiner has previously asserted that the use of the term "structural homologs" was not intended to directly compare different primer sequences that bind to a common target sequence but rather that equivalency has been recognized in the prior art since the cited primers and probes are homologous to sequences taught by the prior art of Hemauer and are therefore functionally equivalent to other primers and probes that target the same sequence. These definitions of “equivalents” and “structural homologs” is based on case law and are different from the biological definition of these terms, wherein nucleic acid homologs share identical nucleotide sequences. In the current situation, the claimed oligonucleotides and those taught by the prior art share a common function by amplifying and detecting a common region of nucleic acid sequence.

The Examiner also relied on Harder as a primary reference since this reference teaches detection of parvovirus B19 using primers and adjacent-binding donor/acceptor probes for use in a real-time PCR assay. Though Harder does not teach any of the specific primers or probes cited in claim 4, the reference does teach primers and adjacent-binding donor/acceptor probes that bind within nucleotides 1420 to 1631 of the NS1 region. Furthermore, though Hemauer also fails to teach the specific primers or

probes cited in claim 4, this reference teaches the NS1 region spanning genome positions 1924-2317 that include the binding sites of the claimed oligonucleotides, as well as a primer set taught by Hemauer that resides within 307 bases of the claimed primer sequences. Though Harder does not teach the NS1 sequence itself, both Harder and Hemauer teach primers that can amplify this sequence, and therefore it is obvious to combine the teachings of Harder for diagnostic detection of parvovirus B19 in a sample with a teaching such as Hemauer that provides the NS1 sequence that can be used for primer and probe design.

Therefore, the claimed primers and probes are prima facie obvious over the cited art references in the absence of secondary considerations. No evidence of secondary considerations, such as unexpected or superior results that may be obtained using the claimed oligonucleotides in comparison to the prior art, has been presented.

Motivation to combine

The Federal Circuit has recently provided a detailed explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> “Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent

> any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years of experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to prepare DNA fragments by homopolymer tailing for purposes of attaching adapters. Some of the listed motivations of Dystar, to result in a cleaner, more efficient, faster, cheaper and more durable assay, would motivate the ordinary practitioner to perform fragment labeling and adapter attachment in a more efficient manner.

Appellant argues that the Examiner has failed to indicate how one of ordinary skill in the art would be motivated to modify the teachings of Schmidt or Harder simply because others also amplify areas of the NS1 region. Appellant argues that since the NS1 region spans greater than 2 kilobases, an almost infinite number of possible alternative oligonucleotide design options are available, and that it is unreasonable to design and test every possible oligonucleotide in this region. Furthermore, Appellant argues that there is no motivation provided in any of the cited references to make primers in different regions, and that the prior art does not indicate a need to improve or change these primers. Appellant further argues that Hemauer teaches amplification of other regions in addition to the NS1 region that are more conserved than the NS1 region, thus teaching away from the regions targeted by Schmidt. While Schmidt does

not teach the claimed primers and probe, the reference teaches amplification of a region spanning from nucleotides 2030 to 2171, which overlaps significantly with the region amplified using the claimed primers (nucleotides 2044-2174). Based on primer and probe design software available at the time of the invention for real-time PCR assays, the small region of NS1 targeted by Schmidt would significantly limit the number of possible primer/probe combinations that could be designed. Though Hemauer teaches amplification of both NS1 as well as other regions of parvovirus B19, there are not large differences in sequence variability throughout the genome (see Table 1). In fact, the region from nucleotides 2020 to 2240 that spans the region targeted by the claimed primers and those of Schmidt is described as being "relatively conserved" (Hemauer, p. 1783, column 2, lines 6-11). Therefore, since the region targeted by Schmidt resides in a relatively conserved region, one of skill in the art would not be motivated to look beyond this region. However, though the assay taught by Schmidt is highly reproducible, quantification using the real-time PCR assay was only reproducible when the sample contained greater than 1000 target copies/ml of sample (Schmidt, p. 230, column 1, last three lines to first line of column 2). Therefore, one of skill in the art would recognize that improvements to the assay, such as to increase the sensitivity of the assay, may require further optimization, including the testing of additional primer/probe sets in the NS1 region.

Harder, like Schmidt, does not teach the claimed primers and probe, but does teach amplification of a region spanning from nucleotides 1420 to 1631 of a highly conserved region of NS1 and also teaches software for designing the primers and

probes for detection of the amplicon (p. 4414, column 2, third paragraph). Based on the available software, the small region of NS1 targeted by Harder would significantly limit the number of possible primer/probe combinations that could be designed. Though the assay taught by Harder is highly sensitive, quantification using the real-time PCR assay was only accurate when the sample contained greater than about 5 copies of target sequence (Harder, p. 4415, column 2, first full paragraph and Figure 2). Therefore, one of skill in the art would recognize that improvements to the assay, such as to increase the reproducibility of the assay for quantification at low target levels, may require further optimization, including the testing of additional primer/probe sets in the NS1 region.

Appellant then argues that the Examiner relies on the court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), in which the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103(a), particularly "when there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp". Appellant argues that a problem inherent in the prior art has not been identified, nor has a design need or market pressure to solve that problem been shown, along with the necessary finite number of identified, predictable solutions to the problem. As discussed above, Schmidt and Harder both teach the design of a primer/probe set targeting a specific region of NS1 that are relatively conserved. As also noted by Schmidt, since there are no applicable *in vitro* infectivity assays available for detection

of paravovirus B19, PCR-based assays are essential for determining the level of contamination in samples such as blood components (p. 229, column 1, second paragraph). While Schmidt teaches a real-time based PCR assay that is highly reproducible and sensitive down to about 1000 genome copies/ml of sample (Schmidt, p. 230, column 1, last three lines to first line of column 2), one of skill in the art would recognize that improvements to the assay are possible, such as the design of additional primer/probe sets in the NS1 region. Though a large number of potential primers and probes could be designed for the conserved region of NS1, primer and probe design tools available to the ordinary practitioner at the time of the invention are designed to select sequences within a given target that are most likely to succeed in PCR, including real-time PCR.

Furthermore, in a recent Board decision, the "obvious to try" test was deemed particularly relevant with regard to nucleotide sequences, as summarized by the Board in Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007):

> "General rule that it is improper to use prior art disclosure of particular protein, together with methods of isolating cDNA disclosed in other references, to reject claims drawn to specific nucleotide sequences on ground of obviousness is not viable to extent it rejects "obvious to try" test, since "obvious to try" may be appropriate test in more situations than previously contemplated; in present case, rule does not preclude finding that claimed nucleotide sequences encoding natural killer cell activation inducing ligand ("NAIL") polypeptide would have been obvious to person of ordinary skill in art based on prior art patent's disclosure of "p38" protein, which is same protein as NAIL, and patent's express teachings on how to isolate p38 cDNA by conventional techniques, since "problem" facing persons in art was isolation of NAIL cDNA, and there were limited number of methodologies for doing so, since skilled artisan would have had reason to try these methodologies with reasonable expectation that at least one would be successful, and since isolating NAIL cDNA thus was product ordinary skill and common sense, not innovation."

The Board emphasizes that the "obvious to try" test may be an appropriate test in more situations than previously contemplated, and is now considered more relevant with regard to claimed polynucleotides than *In re Deuel*.

Based on our findings and those of the Examiner, at least one of Appellants' claimed polynucleotides would have been obvious to one of ordinary skill in the art at the time Appellants' invention was made. Regardless of some factual similarities between Deuel and this case, Deuel is not controlling and thus does not stand in the way of our conclusion, given the increased level of skill in the art and the factual differences. See In re Wallach, 378 F.3d 1330, 1334, 71 USPQ2d 1939, 1942 (Fed. Cir. 2004) ("state of the art has developed [since] In re Deuel").

Appellants heavily rely on Deuel. (See, e.g., Br. 19.) To the extent Deuel is considered relevant to this case, we note the Supreme Court recently cast doubt on the viability of Deuel to the extent the Federal Circuit rejected an "obvious to try" test. See KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, ___, 82 USPQ2d 1385, 1394, 1396 (2007) (citing Deuel, 51 F.3d at 1559). Under KSR, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007). This reasoning is applicable here. The "problem" facing those in the art was to isolate NAIL cDNA, and there were a limited number of methodologies available to do so. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. Thus, isolating NAIL cDNA was "the product not of innovation but of ordinary skill and common sense," leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it.

Thus, since the claimed primers and probe simply represent structural homologs of the sequences taught by Schmidt and Hemauer or Harder and Hamauer, which are 100% derived from sequences of parvovirus B19, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations. As shown in Table 1 of Example 2 in the specification, the claimed primers are capable of accurately detecting about 10-100 genome copies/ml of a diluted control sample, while Schmidt reported similar sensitivities in repeated tests using dilutions of a similar viral standard (see p. 230, column 2, third paragraph to column 1, first paragraph). Likewise, Harder reported detection down to about 5 genome copies per sample (Harder, p. 4415, column 2, first full paragraph and Figure 2). Thus, there is no evidence that using the claimed primers and probes results in unexpected or superior results relative to the known art at the time of the invention.

Appellant then argues against the Examiner's assertion that the teachings of Lowe provide guidance for designing primers that one of skill will have a reasonable expectation of success in amplification of the NS1 region using equivalents of the claims primers, citing the Examiner's incorrect use of "equivalents" in the context of nucleic acid sequences, and the lack of teaching and motivation cited in the art in selecting the particular region of NS1 to design the claimed sequences. With regard to the issue of equivalence of the primers, MPEP 2144.06 notes, "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." While the claimed primers are not directly taught by the cited art, the evidence set forth by Lowe still provides an ordinary practitioner with a reasonable expectation of success for successful amplification of a known sequence, after initially identifying candidate primers. As previously stated, Schmidt and Hemauer, as well as Harder and Hamauer, provide the necessary guidance to one of ordinary skill in the art for the design of primers and probes for detection of parvovirus B19 by PCR.

Therefore, the rejections using Schmidt in view of Hemauer and further in view of Lowe or Harder in view of Hemauer and further in view of Lowe teach or suggest all the

elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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